

Value of Early Referral to Fertility Preservation in Young Women With Breast Cancer

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ABSTRACT

Purpose

To determine whether early referral to reproductive specialists improves fertility preservation (FP) outcomes and reduces delay in adjuvant treatment in young women with breast cancer.

Patients and Methods

A secondary analysis of a prospective database of patients with breast cancer undergoing ovarian stimulation (OS) for FP by oocyte or embryo cryopreservation was performed.

Results

Of the 154 patients, 93 met the inclusion criteria (mean age, 35.2 ± 4.4 years). Thirty-five of the 93 patients were referred before breast surgery (PreS), and 58 patients were referred after surgery (PostS). The time periods from initial diagnosis (ID) to initiation of OS (42.6 ± 27.7 days for PreS v 71.9 ± 30.7 days for PostS; $P < .001$) and from ID to initiation of chemotherapy (83.9 ± 24.3 days for PreS v 107.8 ± 42.9 days for PostS; $P = .045$) were significantly shorter for the PreS group versus the PostS group. Nine (25.7%) of 35 patients in the PreS group versus one (1.7%) of 58 patients in the PostS group were able to undergo two FP cycles ($P < .001$), resulting in an increased yield of oocytes in the PreS group (18.2% [93 of 511 oocytes] v 0.6% [five of 800 oocytes], respectively; $P < .001$) and embryos (17.2% [40 of 233 embryos] v 0.6% [two of 357 embryos], respectively; $P < .001$). Patients who had an oocyte retrieval within 5 weeks of the surgery were able to complete a second cycle within 9 weeks of the surgery.

Conclusion

FP referral before breast surgery enables earlier initiation of cryopreservation cycles and chemotherapy and, when appropriate, multiple FP cycles. Women who can undergo multiple cycles may be at advantage for FP because of a larger number of oocytes or embryos cryopreserved. This is the first study demonstrating the benefit of early FP referral in patients with cancer.

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INTRODUCTION

Excluding skin cancers, breast cancer is the most frequently diagnosed cancer in women and the most common malignancy encountered during reproductive ages.¹ Because of improvement in diagnostic and therapeutic strategies, an increasingly larger number of women are surviving with breast cancer. As a result, quality-of-life issues, including issues involving fertility preservation (FP), have gained significant importance in cancer care.

A number of FP strategies have been developed, including embryo, oocyte, and ovarian tissue freezing. Both embryo and oocyte freezing require ovarian stimulation (OS) with gonadotropins, which results in excessive levels of estrogen production. To reduce the estrogen exposure during OS in women with breast cancer, we developed novel protocols using aromatase inhibitors as an ovarian stim-

ulant.² Embryo cryopreservation is an established assisted reproduction technique, and for single women, oocyte freezing is an alternative.³⁻⁵ However, because OS must be started within the first 4 days of the menstrual cycle to be effective and requires approximately 2 weeks for completion, early referral is crucial to avoid a delay in chemotherapy.

The American Society of Clinical Oncology (ASCO) issued guidelines recommending that young patients with cancer be referred to reproductive specialists for FP as soon as possible after cancer diagnosis.³ However, that recommendation is based solely on expert opinion and lacks data for its direct support. The purpose of this study was to determine whether early referral to reproductive specialists, as recommended by the ASCO guidelines, improves FP outcomes and reduces the delay of adjuvant treatment in young women with breast cancer.

PATIENTS AND METHODS

We secondarily analyzed a prospectively collected database from the Controlled Ovarian Stimulation Treatment with Letrozole Supplementation Study (COST-LESS)^{2,6-8} of 154 women with breast cancer undergoing OS for FP by embryo or oocyte cryopreservation, which was approved by the institutional review board. The inclusion criteria were as follows: availability of complete data on the date of initial diagnosis (ID), first FP consultation (FPC), surgery date (mastectomy/lumpectomy), initiation of OS, and the date of oocyte retrieval; age ≤ 45 years; breast cancer stage \leq stage III; no prior chemotherapy or ovarian surgery; and no prior history of infertility. The exact dates were available in 108 patients, and of those, 93 met all inclusion criteria. Although this was not a reason for exclusion, exact dates of initiation of chemotherapy were available in 50 of 93 patients.

In cycle 1, there were 10 cycles of oocyte freezing, 76 cycles of embryo freezing, five cycles of both embryo and oocyte freezing, and two cancellations. In cycle 2, there was one cycle of oocyte freezing, eight cycles of embryo freezing, and one cancellation.

Statistical analysis was performed with the SPSS 17 for Windows package (SPSS, Chicago, IL). Continuous data (presented as mean \pm standard deviation) were analyzed by *t* test. The nonparametric data were analyzed using the Mann-Whitney *U* test. Levene's test of homogeneity of variances ($P < .01$) and the Kolmogorov-Smirnov test of normality ($P < .01$) were performed to choose the appropriate statistical test. χ^2 and Fisher's exact test were performed to analyze the relation between two categorical variables. When $P < .05$, the difference was considered statistically significant in all statistical tests. Multiple linear regression of the defined time intervals was used to evaluate the clinical characteristics (Table 1); estrogen receptor (ER), progesterone receptor (PR), *HER2/neu*, and *BRCA* status; and their pairwise interaction terms.

Table 1. Comparison of Clinical Characteristics of Women Referred for Fertility Preservation Before and After Breast Surgery

| Characteristic | PreS (n = 35) | PostS (n = 58) | P |
|------------------------------|------------------|-------------------|------|
| Age | | | NS |
| Mean | 34.5 | 35.4 | |
| SD | 3.7 | 4.4 | |
| Cancer stage, % | | | NS |
| In situ | 2.9 | 1.7 | |
| I | 45.7 | 48.3 | |
| II | 28.6 | 32.8 | |
| III | 2.9 | 3.4 | |
| Unknown | 20.0 | 13.8 | |
| Estrogen receptor status | | | .042 |
| Positive | 57.1 | 86.2 | |
| Negative | 22.9 | 10.3 | |
| Unknown | 20.0 | 3.4 | |
| Progesterone receptor status | | | NS |
| Positive | 42.9 | 63.8 | |
| Negative | 31.4 | 24.1 | |
| Unknown | 25.7 | 12.1 | |
| <i>HER2/neu</i> | | | NS |
| Positive | 17.1 | 32.8 | |
| Negative | 54.3 | 50.0 | |
| Unknown | 28.6 | 17.2 | |
| <i>BRCA</i> | | | NS |
| Positive | 14.3 | 13.8 | |
| Negative | 42.9 | 39.7 | |
| Unknown | 42.9 | 46.6 | |

Abbreviations: PreS, referred before breast surgery; PostS, referred after breast surgery; NS, not significant; SD, standard deviation.

Table 2. Comparison of FP Outcomes in the First Cycle Between the PreS Group and the PostS Group

| Outcome | PreS (n = 35) | | PostS (n = 58) | | P |
|------------------------------|------------------|-----|-------------------|-----|----|
| | Mean | SD | Mean | SD | |
| No. of oocytes harvested | 11.9 | 9.3 | 13.7 | 8.5 | NS |
| No. of oocytes cryopreserved | 8.3 | 2.9 | 13.4 | 6.2 | NS |
| No. of oocytes fertilized | 6.5 | 4.9 | 7.5 | 4.6 | NS |
| No. of embryos cryopreserved | 6.4 | 4.7 | 7.6 | 5.1 | NS |

Abbreviations: FP, fertility preservation; PreS, referred before breast surgery; PostS, referred after breast surgery; SD, standard deviation; NS, not significant.

RESULTS

The mean age of the study population was 35.1 ± 4.1 years (range, 24 to 45 years). Thirty-five of the 93 patients were referred and evaluated before breast cancer surgery (PreS), and 58 patients were referred after surgery (PostS). PreS and PostS groups were similar in terms of mean age; cancer stage; and PR, *HER2/neu*, and *BRCA* status, with the exception that the PostS group had a higher percentage of ER-positive tumors ($P = .042$; Table 1).

The mean dose of gonadotropins used ($1,809.5 \pm 739.7$ U ν $1,725.7 \pm 738.1$ U in the PreS ν PostS group, respectively; $P = .676$) and number of oocytes harvested, oocytes cryopreserved, oocytes fertilized, and embryos cryopreserved were similar between the two groups (Table 2), indicating that OS cycles were performed similarly regardless of whether the referral occurred before or after surgery. Likewise, there was no significant difference in the length of time period from ID to surgery date, FPC to OS, or OS to oocyte retrieval between the two groups (Table 3), indicating that the groups were otherwise managed similarly by the oncologists and the FP team.

In contrast, the time periods from ID to OS (42.6 ± 27.7 days for PreS ν 71.9 ± 30.7 days for PostS; $P < .001$) and from ID to chemotherapy (83.9 ± 24.3 days for PreS ν 107.8 ± 42.9 days for PostS; $P = .045$) were significantly shorter for patients who were referred before surgery versus after surgery (Fig 1). This indicates that

Table 3. Comparison of Time Periods Between Women in the PreS Group and Women in the PostS Group

| Period | PreS (No. of days) | | PostS (No. of days) | | P |
|--------------------------------------|-----------------------|------|------------------------|------|--------|
| | Mean | SD | Mean | SD | |
| ID to OS | 42.6 | 27.7 | 71.9 | 30.7 | < .001 |
| ID to BS | 28.6 | 20.6 | 33.4 | 24.3 | NS |
| FPC to OS | 25.1 | 26.0 | 15.2 | 13.0 | .088 |
| OS to OR | 11.5 | 1.5 | 11.5 | 1.6 | NS |
| ID to chemo (single cycle only) | 83.9 | 24.3 | 107.8 | 42.9 | .045 |
| ID to chemo (including second cycle) | 88.8 | 45.7 | 107.4 | 42.3 | .058 |

Abbreviations: PreS, referred before breast surgery; PostS, referred after breast surgery; SD, standard deviation; ID, initial diagnosis of breast cancer; OS, initiation of ovarian stimulation; BS, breast surgery; NS, not significant; FPC, first fertility preservation consultation; OR, oocyte retrieval; chemo, initiation of chemotherapy.

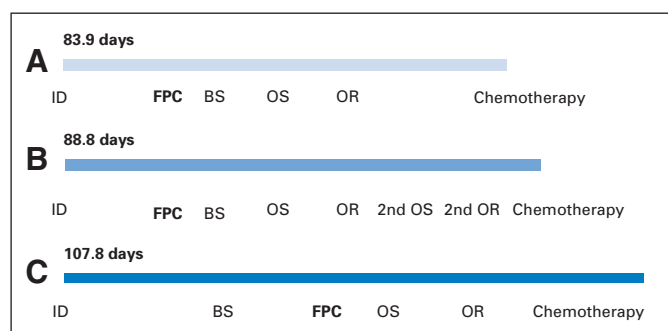


Fig 1. Comparison of referral patterns to fertility preservation (FP) in patients with breast cancer. Referral before breast surgery results in the initiation of chemotherapy on average 3 weeks earlier in (A) single FP cycles, as well as when the data from (B) double cycles are included, compared with (C) patients referred after breast surgery. This additional time enables multiple cycles of FP, if desired, in a shorter time period before chemotherapy compared with referral after breast surgery. Number of days indicates time from initial diagnosis with breast cancer (ID) to initiation of chemotherapy. FPC, first fertility preservation consultation; BS, breast surgery; OS, initiation of ovarian stimulation; OR, oocyte retrieval.

early referral before breast surgery results in earlier commencement of FP treatment and a shorter delay in initiating adjuvant treatment.

Moreover, a significantly larger proportion of patients in the PreS group (nine of 35 patients; 25.7%) compared with the PostS group (one of 58 patients; 1.7%) were able to undergo an additional cycle of FP ($P < .001$). This resulted in an 18.2% (93 of 511 oocytes) versus 0.6% (five of 800 oocytes) increase in the total oocyte yield ($P < .001$) in the PreS group versus the PostS group. Likewise, the number of embryos cryopreserved increased by a significant margin ($P < .001$) in the PreS group (17.2%; 40 of 233 embryos) compared with the PostS group (0.6%; two of 357 embryos; Table 4).

Patients who underwent first oocyte retrieval within 5 weeks of the surgery, regardless of whether the FPC occurred before or after surgery, were able to complete a second cycle within 9 weeks of the surgery. Even with the data from double cycles included, the time period from ID to chemotherapy trended shorter in the PreS group compared with the PostS group (88.8 ± 45.7 days v 107.4 ± 42.3 days, respectively; $P = .058$). Regression analysis did not reveal any notable associations between defined time intervals and receptor and *BRCA* status. All possible second-order pairwise terms were evaluated and found to be nonsignificant.

Table 4. Impact of Additional Cycles on FP Outcome

| Outcome | PreS | | PostS | | <i>P</i> |
|---|----------------|------|---------------|-----|----------|
| | No./Total No.* | % | No./Total No. | % | |
| Patients undergoing second FP cycle | 9/35 | 25.7 | 1/58 | 1.7 | $< .001$ |
| Additional No. of oocytes harvested out of total† | 93/511 | 18.2 | 5/800 | 0.6 | $< .001$ |
| Additional No. of unfertilized oocytes cryopreserved out of total | 14/47 | 29.8 | 0/121 | 0 | $< .001$ |
| Additional No. of embryos cryopreserved out of total | 40/233 | 17.2 | 2/357 | 0.6 | $< .001$ |

Abbreviations: FP, Fertility preservation; PreS, referred before breast surgery; PostS, referred after breast surgery.

*Total No. includes both first and second cycles.

†Total No. of usable oocytes harvested regardless of whether the intention was to cryopreserve them unfertilized or as embryos.

DISCUSSION

In this article, we compared two different referral patterns to FP (Fig 1). We concluded that early referral before breast surgery enables women with breast cancer to initiate an FP cycle sooner and undergo multiple cycles of oocyte or embryo freezing, if desired. Women who can undergo multiple cycles are likely to be at an advantage for FP because of the additional number of eggs or embryos generated. Nine of 35 patients who were in the PreS group and, in contrast, only one of 58 patients in the PostS group had a chance to undergo a second cycle, without a delay in chemotherapy beyond 9 weeks after surgery. This delay is generally acceptable because multiple studies have shown no effect on survival or recurrence in patients with breast cancer if chemotherapy is initiated as late as 12 weeks after breast surgery.^{9,10} Strikingly, we also showed that patients in the PreS group initiated chemotherapy on average 24 days earlier compared with patients in the PostS group.

Information on the date of initiation of chemotherapy was available on a smaller sample size (50 of 93 patients). Nevertheless, the date of initiation of OS was available for all patients. OS was initiated on average 30 days earlier (Table 2) in the PreS group than in the PostS group, consistent with the 24-day earlier initiation of chemotherapy in the same group.

Furthermore, the mean time interval from ID to breast cancer surgery was 28.6 days in the PreS group and 33.4 days in the PostS group; this difference was not statistically significant. Hence, early referral to FP resulted in earlier initiation of chemotherapy without a significant delay in breast surgery.

Women in the PreS group were more likely to have an ER-negative tumor. Although our database was not designed to analyze the factors that influenced the oncologists' decision making in referring patients to FP, ER status might have affected that decision. It is possible that oncologists felt greater urgency to initiate women with ER-negative tumors on chemotherapy sooner, which prompted earlier referral to FP. However, we believe this is unlikely because receptor status would not have been available in the majority of patients before breast surgery.

In keeping with the ASCO guidelines published in 2006, the American Society for Reproductive Medicine also recommends attention to the impact of cancer treatments on fertility and quality of life for younger cancer survivors.^{3,11} However, most recent studies have indicated that still less than half of physicians routinely refer patients of childbearing age with cancer to reproductive specialists.¹² A recent study reported that although most oncologists recognize the importance of discussing infertility risks after cancer treatment, few actually discuss FP with their patients.¹³ Our data add a new dimension to the findings of these studies; this dimension is the timing of referrals. Emphasizing referral as early in the process as possible to maximize the likelihood of success is as important as encouraging oncologists to refer young people with cancer to FP counseling.

Our current live birth rate per frozen embryo transfer cycle with the transfer of two embryos is approximately 38%. Because in our cohort the mean number of embryos cryopreserved including both cycles is approximately eight embryos (7.7 ± 5.2 embryos) and given the 75% survival rate after thaw, this may allow approximately three trials of embryo transfer, translating into a cumulative projected live birth rate of 76%. Data on success from frozen oocytes are still limited

because the technique is still investigational. Oocytes that were frozen with techniques predating 2005 resulted in live birth in 21.6% of embryo transfers.¹⁴ We recently updated our database (unpublished data), which indicates that the likelihood of live birth per embryo transfer might be approaching that with frozen embryos. Given the heterogeneity of the data in the literature, however, we counsel our patients that a frozen oocyte is 50% less likely to result in a live birth compared with a fresh oocyte from a woman of similar age. Regardless, with modern technology, both embryo and oocyte freezing seem to be associated with reasonable chances of preservation of fertility.

A number of specialties are involved in the care of women with breast cancer, which may increase the likelihood that they may be informed about FP options. However, because medical oncologists are usually involved with the care later in the process, breast surgeons, interventional radiologists, and other specialists who take part in the ID may carry more weight in ensuring earlier referral to FP.

In summation, early referral before breast surgery enables women with breast cancer to undergo OS for FP earlier and start chemotherapy on average 3 weeks earlier than if referral occurs after surgery. If needed, patients who are referred before surgery can use this additional time to undergo multiple cryopreservation cycles and preserve a larger number of eggs and embryos.

The prospective database that was used in this study was limited because it was not originally designed to analyze referral patterns. However, our study is seminal because to our knowledge, it is the first to quantify the benefits of early referral to FP. Our findings support a need for shift in practice for oncologists treating young women with breast cancer who wish to try to preserve their fertility. It is clear that

referring these women to a reproductive endocrinologist before surgery, rather than afterward, can optimize chances to cryopreserve oocytes or embryos without any delay of breast surgery or initiation of chemotherapy. This is an important finding that may shift the responsibility for these referrals from the medical oncologist to the breast surgeon. Early referral of patients with breast cancer to reproductive specialists before breast surgery is an essential step to increase the likelihood of obtaining a sufficient quantity of oocytes for FP without a delay in breast cancer treatment. Practitioners should adhere to the 2006 FP guidelines issued by ASCO.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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Administrative support: Kutluk Oktay

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